Predictors of 1-Year Mortality inpatients withNon-invasive HomeMechanicalVentilation.

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Abstract-Background: Home mechanical ventilation (HMV) is broadly and increasingly accepted as a treatment option for chronic respiratory failure, which most often occurs in chronic obstructive pulmonary disease (COPD), restrictive lung diseases, obesity-hypoventilation syndrome and neuromuscular disorders such as amyotrophic lateral sclerosis (ALS), Duchenne, etc. Thus, this project is aimed to measure the one-year mortality of patients using home mechanical ventilation according to their diagnosis. **Objectives-**All-cause one-year mortality rate of patients with noninvasive mechanical home ventilation (HMV) and predictors of mortality. **Methods-**A retrospective observational cohort study was performed on all patients received home mechanical ventilation (HMV) during the period (Jan-1996-July-2013) in the region of Limburg, Netherlands. **Results-**A total of 761 patients were enrolled in this study. Mean age was 60 (18-91) years old, and 455 patients (59,8%) were male. In total 134 patients (17,60%) have died during the first year of HMV. We found that underlying disease are predictors of mortality. In ALS group 58 patients (43,30%) died, COPD group 35 patients (26,01%), thesleep apnea group 15 patients (11,20%), and 6 (4,50%) for both Restrictive group and COPD with other pulmonary related diseases group. Other predictors of mortality were AGE (p=0,018, Exp(B): 1,029, 95% C.I for Exp(B): 1,005-1,054), PCO2 >6.0 kPa (p=0,029, Exp(B): 1,191, 95% C.I for Exp(B): 1,018-1,393. FVC in liter (p=0,42, Exp(B)= 1,605, 95% C.I for Exp(B)= 1,017-2,533. FVC predicted (p=0,011, Exp(B)=0,972, 95% C.I for Exp(B)= (0,951-0,994). **Conclusion-**Age, PaCO2, FVC and the underlying disease are predictors for increasing mortality within the first year of starting non- invasive home mechanical ventilation**.**

Key Words-Non-invasive home mechanical ventilation (NIV), Mortality, Predicators, Diagnosis

INTRODUCTION

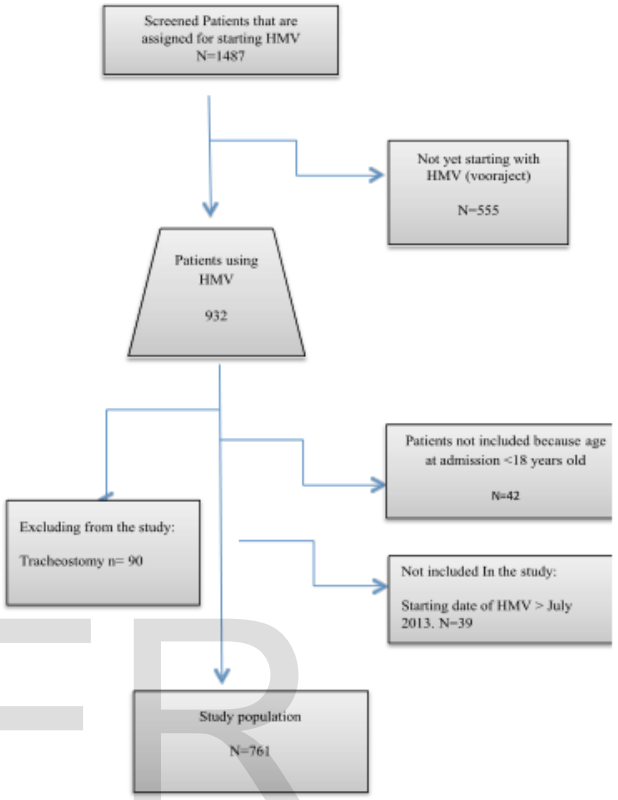
Home mechanical ventilation (HMV) is broadly and increasingly accepted as a treatment option for chronic respiratory failure, which most often occurs in chronic obstructive pulmonary disease (COPD), restrictive lung diseases, obesity-hypoventilation syndrome and neuromusculardisorders. The rising costs of hospital care the advent ofcommercially available noninvasive masks has fueled greater demand for HMV(1) Importance for the initiation of HMV is the presence of symptoms of respiratory failure and the finding of hypoventilation, most importantly hypercapnia. Non- invasive home mechanical ventilation (NIV) can be administered using several facial masks whereas invasive homemechanical ventilation is performed via a tracheostomy. Indications of installing HMV are disorders of the respiratory pump (neuromuscular diseases, chest wall diseases, spinal cord injury), obstructive diseases of the airway (craniofacial abnormalities, hypotonic, obesity), parenchymal lung disease (bronchopulmonary dysplasia (BPD), cystic fibrosis), disorders of control of respiration (Congenital central hypoventilation syndrome) and sleep disturbance (Central or obstructive, apnea or hypopnea). In addition, home mechanical ventilation must be organized around a specialized respiratory care centers with expertise inpatient selection, the initiation and the control of home mechanical ventilation. HMV has been shown to improve health-related quality of life (QOL) of patients with chronic respiratory failure. Long-term survival is improved in most patient groups, even though the long-term prognosis is often severely limited(2). Moreover, patients on home mechanical ventilation with progressive neuromuscular disease such as Duchenne muscular dystrophy and amyotrophic lateral sclerosis (ALS) can alsoderive prolongation of life, palliation of symptoms and an improvement in quality of life(3). Non-invasive mechanical ventilation (NIV) is commonly suggested for patients with amyotrophic lateral sclerosis (ALS)(4). Thus, identifying factors that are related to a rapid deterioration of respiratory function should be considered of critical importance. One study concluded that, they found by far the poorest survival rate in the ALS patients with only 5% alive after 5 years. No factors were associate with a greater hazard for death in the ALS patients, however negative predictors for survival was age(5). The survival of patients with kyphoscoliosis receiving HMV was better than that of patients treated with LTOT alone. We suggest HMV and not oxygen therapy alone as the primary therapy for patients with respiratory failure due to kyphoscoliosis, regardless of gender, age, and the occurrence of concomitant respiratory diseases(6) Furthermore, there is a difference in survival or success outcome between diagnosis/ indications. And we would like to find out more about predictors for successful mechanical home ventilation or survival. Thus, this project is aimed to measure the short and most importantly long-term outcome of patients using home mechanical ventilation according to their diagnosis.

MATERIAL AND METHODS

Data of patients was collected from medical files and electronic patient records from the SAP system of AZM hospital, Maastricht, The Netherlands, and also from the data collection system of the center of home mechanical ventilation (CTBM). Lung function result (FVC in liter, FVC predicated) and arterial blood gases of patients were taken before starting HMV. In some patients we could not find any information in some patients' files about arterial blood gases, lung function tests and other variables, so for this reason we have recorded above each set of variables the number and the percentages of patients whom we have collected their data of that specific set of variables. A retrospective observational cohort study was performed on all patients who have received home mechanical ventilation (HMV) in the Mechanical Ventilation. All-cause one-year mortality rate of patients with noninvasive mechanical home ventilation (HMV). Predictors of mortality in patients using HMV. We recorded patients' survival, arterial blood gases and lung function (FVC in liter and predicted) before starting HMV, the status of using the ventilators, if patients stopped or not, and the reason of stopping if recorded. i.e. All patients treated by home mechanical ventilation during the period (Jan-1996-July-2013) in the region of Limburg, The Netherlands, were retrospectively included in a computerized database. In this study we analyzed only patients over the age of 18 years when starting HMV. Patients with tracheostomies were not included in this analysis. In total of 761 patients were included in the study. The flow chart of patients' selection is shown in Fig1. Patients were divided into 6 groups according to the underlying diagnosis as the following. COPD group (in the register defined as chronic obstructive pulmonary disease with no other pulmonary diseases), COPD with other related pulmonary diseases group (Asthma n=5, Diaphragmatic Paralysis n=1, OSAS/CSAS n=45, OHS n=15, CF n=12, congenital kyphoscoliosis n=2),

Amyotrophic lateral sclerosis (ALS) group, Sleep apnea syndrome group (OSAS/CSAS with restrictive lung disorders but without OHS), NMD group (Neuromuscular disorders other than ALS, i.e. mainly patients with progressive and slow NMD,i.e. Duchenne n=28, Gullain-Barre n=4, Mysthenia gravis n=6, Myotonic dystrophy n=76, Progressieve spinal muscular atrophy N=14), and Restrictive lung diseases group (Patients with OHS, Paralysis, kyphoscoliosis, Diaphragmatic Paralysis, Sarcoidosis, chest wall deformities and pulmonary fibrosis).

Figure 1: Flowchart of patients' selection.



Data analysis was carried out using descriptive and analytical statistics through SPSS version 20. Patient characteristics (Univariate analysis) were tested by descriptive statistics, explore and frequencies. Then variables were tested for normality by Kolmogorov-Smirnov and Sapiro-Wilk tests. After that Kruskal Walis test was used for obtaining Univariate analyses of not normally distributed continuous variables while one-way ANOVA test was used for obtaining the Univariate analysis of the normally distributed variables. After obtaining all the Univariate analyses of all the variables we have included parameters which were significant (P-value= 0,05) in Univariate analysis were taken as possible predictors of short- and long-term mortality in a logistics regression analysis into the multivariate analysis. We reported the result as median (interquartile range for continues not normally distributed data, mean +- SD for continues normally distributed data and percentage % for discrete variables. Comparison in between groups was done by splitting file data according to diagnosis. S Survival analysis was done by using Kaplan–Meier curve and Log Rank.

RESULT

In table 1, patients' characteristics and lung functions of the patients are summarized. Patients were divided into 6 main groups according to their diagnosis; COPD n=(139), COPD+ comorbidity (80), ALS n=(110), NMD =(128), Sleep apnea disorders n=(224), Restrictive Lung Diseases n=(80). In total 761 patients, who started HMV between (1996-2013) and were included in this study.

Table 1: Patient's characteristics

Variables	All (n=761)	COPD (n=139)	COPD with other sleep related disorders N=(80)	ALS (n=110)	Sleep Apnea syndrome (n=224)	NMD n=(128)	Restrictive Lung diseases n=(80)	P-value
Age at starting HMV	60 (18-91)	63(41-82)	65(18-85)	64(25-80)	59 (18-91)	51 (18-81)	60 (18-83)	<0,001
Sex								
Male	455 (59,8)	62 (44,6)	46 (57,5)	73 (66,4)	160 (71,4)	73 (57)	41 (51,3)	
Female	306 (40,2)	77 (55,4)	34 (42,5)	37 (33,6)	64 (28,6)	55 (43)	39 (48,8)	NS
FVC in Liter*	2,37 ±1,10	2,10±0,77	2,41 ±1,02	2,33 ±1,08	3,00±1,20	2,09±0,83	1,56±0,86	<0,001
FVC predicted% *	63,84 ± 23,87	64,94 ±19,23	67,14±23,04	60,93 ±22,38	75,34 ±24,27	53,63 ±20,60	48,35 ±21,131	<0,001

Values are presented as N (%), median (interquartile range) or *mean ± SD. HMV=home mechanical ventilation; FVC= forced vital capacity; COPD= chronic obstructive pulmonary disease; ALS= Amyotrophic lateral sclerosis; NMD= neuromuscular disorders.

Age at starting HMV between groups significantly differs, with NMD patients significantly younger, compared to the other groups. Median age of all patients was 60 (18-91) years old, and 455 patients (59,8%) were male. No difference in gender was observed between the groups. Overall, patients had a mild FVC in liters (2,37 ±1,10) and predicted FVC (63,84 ± 23,87). The Spirometry values (Table 1), significantly differ in between the groups, P <0,001. Sleep apnea group has the highest value compared to other, (FVC in liter 3,00±1,20) and (predicted FVC 75,34 ±24,27). On the other hand, the lowest values were recorded in the restrictive group, (FVC in liter 1,56±0,86) and (predicted FVC 48,35 ±21,131), also NMD group has a low predicated (FVC 53,63 ±20,60). Arterial blood gases analysis for all patients is shown in (table 3). All patients have a normal PH value of 7,40 (7,00-7,61) and a slightly high PaCO2 6,30 (1,70-17,00), a lower PaO2 value 8,60 (2,80-20,2), a slightly high bicarbonate 28,20 (13,10-50,00), normal base excess 2,30 (-9,00-18,00) and saturation of 93 (55,00-99,00). Blood gases were significantly different in between the groups. COPD group has the highest PaCO2 7,45. Table 2 shows the mortality of all patients who have had HMV. In total 134 patients (17,60%) have died during the first year of HMV. A significant difference in the 1-year mortality was found between the two groups (p<0,001). It can be clearly seen that the ALS group has the highest 1-year mortality rate among the other groups, 58 patients (43,30%) died which represents almost halve of the group population.

Table 2: 1-year mortality

Variables	ALL	COPD	COPD with other diseases	ALS	Sleep Apnea syndrome	NMD	Restrictive	P-value
First year mortality	134 (17,60 %)	35 (26,01 %)	6 (4,50 %)	58 (43,30 %)	15 (11,20%)	14 10,40%)	6 (4,50%)	≤0.001

1-year mortality of all patients. Note: data is presented as N(%)

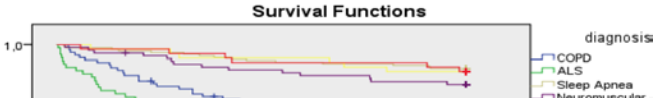
In COPD group 35 patients (26,01%), the sleep apnea group 15 patients (11,20%), and 6 (4,50%) for both Restrictive group and COPD with other pulmonary related diseases group. Kaplan-Meier survival curves for all-cause mortality according to diagnosis at 1 year of home mechanical ventilation are shown in figure 2. The Log Rank (Mantel-Cox) is (46,099) p<0,001. The median of Charlson-indix score was 4,00 (0-12) and the most common comorbidities were Diabetes Mellitus, 136, Heart Failure 88, Myocardial infarction45, CVD 41, Non-malignant tumor 29, Chronic kidney diseases 27, PVD 18, Malignancy 15. The univariate analysis of variables related to 1-mortality of the six groups are diagnosis, age, FVC in liter, PCO2, Act.HCO3 and HBo2 with p-values of (0,001, 0,001, 0,030, 0,002, 0,001and0, 025), respectively. For the multivariate analysis (table 4), the following variables were selected: Age, PH, PaCO2, Act.HCO3, and FVC in liter, FVC predicted%, and gender. From the six groups there were four significant independent predictor of 1-year mortality and that were AGE (p=0,018, Exp(B): 1,029, 95% C.I for Exp(B): 1,005-1,054), PCO2 (p=0,029, Exp(B): 1,191, 95% C.I for Exp(B): 1,018- 1,393. FVC in liter (p=0,42, Exp(B)= 1,605, 95% C.I for Exp(B)= 1,017-2,533. FVC predicted (p=0,011, Exp(B)= 0,972, 95% C.I for Exp(B)= (0,951-0,994).

Table 3: Lab result:

Variables	All 648 (85,15%)	COPD 111 (79,35%)	COPD with other diseases 69 (86.25%)	ALS 95 (86,39%)	Sleep Apnea syncrone 188 (83,92%)	NMD 118 (92,96%)	Restrictive 65 (82,5%)	P-value
PH	7.40 (7,00-7.61)	7,38 (7,00-7,47)	7.39 (7,27-7,47)	7,42 (7,28-7,52)	7,41 (7,17-7,61)	7.39 (7,00-7.54)	7.38 (7,25-7,48)	<0,001
PaCO2	6.30 (1,70-17,00)	7,45 (3,70-16,40)	6.90 (3,60-11,90)	5,80 (3,70-11.60)	5,70 (1,70-18,00)	6.10 (3,00-14,50)	6.85 (4.30-12,00)	<0,001
PaO2	8.60 (2,80-22,2)	8,35 (4,60-14,80)	8.00 (5,00-12,50)	9,70 (5,80-14.70)	8,80 (3,70-20,20)	8.90 (4.68-13,10)	8.30 (2.80-15,80)	<0,001
Act.HCO3	28,20 (13,10-50,00)	32,00 (17,90-50,00)	29,20 (17,60-47,50)	27.40 (21,40-48.10)	26.30 (13,10-29.80)	26,30 (18,50	29,90 (16,10-45,00)	<0,001
BE	2.30 (-9,00-13,00)	5,65 (-5,50-18,00)	1.80(-5,90-9.40)	2,89 (-8,00-9,50)	1,25 (-9,00-3,70)	1.70 (-8,00-9.80)	3.50 (-8,00-9.90)	<0,001
HboO2	93 (55,00-99,00)	92,00 (61,00-98,00)	90,00 (74,00-97,00)	95.00 (82,00-98.00)	84.00 (55,00-58.00)	94,00 (69,00-	91,00 (59,00-97,00)	<0,001

Values are given as median (interquartile range)

Figure 2: Survival (Kaplan-Meier survival curves)



CONCLUSION

This study is meant to illustrate the predictors of the first year mortality in patients using non-invasive home mechanical ventilation (NIV). From this large patients' population that recorded prospectively we have found that underlying diseases are the major predictor factors for mortality. Patients suffering from ALS at all times clearly had the highest probability to die within one year of starting non-invasive home mechanical ventilation (NIV). While COPD group had a lower chance of mortality as twice as ALS. Among the remaining patient groups differences in mortality would be difficult to point out and presents a more uniform pattern. The lowest probability for one-year mortality rates being on patients with restrictive lung disease, sleep apnea disorders and COPD with other pulmonary related disorders. The existing evidence indicates that HMV using NIV is effective in the majority of OHS patients and results in significant improvement in symptoms of somnolence, dyspnea, edema and sleep quality, as well as improvements in gas exchange, sleep architecture and HRQoL(5)(7).COPD only patients and COPD with other pulmonary related disorders seem to be notable in term of mortality, as we have not expected. Because several comorbidities that exist alongside chronic obstructive pulmonary disease (COPD) have been independently linked toa higher risk of mortality in previous study(5).in which 1,664 COPD patients were followed up for a median of 51 months. Among the 79 comorbidities observed in the patients, 12 were significantly and independently associated with an increased risk of death. In previous studies on ALS using home mechanical ventilation there were several survival rates, and there were considerably higher rates compared to our study. The explanation of this may be because that most of patients were on invasive ventilation, whereas this doesn't apply to our population, since all patients were on non-invasive ventilation. One study, however, supports the findings and stated that non- invasive ventilation did not prolong survival in participants with poor bulbar function (21 participants). Evidence from a single randomized trial of non-invasive ventilation in 41 participants suggests that it significantly prolongs survival and improves or maintains quality of life in people with ALS. Survival and some measures of quality of life were significantly improved in the subgroup of people with better bulbar function, but not in those with severe bulbar impairment. Moreover, we found an increased PCO2 >6,00 kPa in patients before staring home mechanical ventilation to be a significant risk factor for mortality in our population p=0,029, Exp(B)=1,191, 95% C.I for Exp(B)= (1,005-1,054). Previous studies have shown that increased PaCO2 is linked to mortality. (7(8, 9)) Looking at the blood we can see that there is a mild respiratory compensation for a metabolic alkalosis. In addition, we also find age to be a significant predictor for mortality, while gender was not. p=0,018, Exp(B): 1,029, 95% C.I for Exp(B): 1,005-1,054). Spirometry parameters are shows to be predictors for mortality in all patients, FVC in liter (p=0,42, Exp(B)= 1,605, 95% C.I for Exp(B)= 1,017-2,533. FVC predicted (p=0,011, Exp(B)= 0,972, 95% C.I for Exp(B)= (0,951-0,994). We believe this study has some limitations include the lack of available data such as lung function test results, comorbidities were not recorded systemically and the diagnosis accuracy. Further research is needed. The strengths are this study was conducted on a large population and the accurate in mortality status.(10)(1

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